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Factors Affecting Tolerance to Digitalis

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A review of factors altering the safety margin between a therapeutic and a toxic dose of digitalis includes the consideration of: 1) clinical conditions to which digitalis action may be undesirable, 2) allergy and hypersensitivity to digitalis, 3) physiologic factors modifying tolerance to digitalis, 4) factors that change the amount of digitalis in the body, 5) nervous and metabolic factors modifying tolerance to digitalis, 6) modifications of digitalis tolerance produced by the status of the myocardium, and 7) modifications of digitalis tolerance produced by diseases of other organs. The problems related to digitalis toxicity are more common than those of resistance to treatment. The most important factors contributing to decreased tolerance and risk of toxicity are: heart disease, poor renal function, hypokalemia and hypothyroidism. The roles of impaired liver function, chronic lung disease, acid-base disturbances, anesthesia, autonomic imbalance, calcium and magnesium are less important and less well established.

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The purpose of this report is to review the factors that cause altered tolerance to digitalis, defined as a change in the safety margin between a therapeutic and a toxic dose or between a toxic and a lethal dose. An increased tolerance signifies the need for larger than customary doses to produce the desired effect. Conversely, a decreased tolerance means that smaller than customary doses will produce an undesirable effect. The understanding of the factors altering the digitalis tolerance and requirements should enhance the safety and effectiveness of digitalis therapy. Many important aspects of this subject, such as the interaction of digitalis with other drugs or the mechanisms underlying therapeutic and toxic effects of glycosides, are discussed elsewhere in this symposium and also in a recent, two part, comprehensive overview of the subject (1,2).

Physicians administering digitalis are much more often confronted with the problems of toxicity than with those of resistance to treatment. To the best of my knowledge, the development of tachyphylaxis to digitalis has not been reported. This may be due to its absence or to the methodologic difficulties in documenting such a phenomenon in clinical practice. A small fraction of patients receiving digitalis may have an unusually high tolerance that cannot be explained by any of the known factors (3). This group includes certain patients with atrial fibrillation or flutter and supraventricular tachycardia who require unusually large doses to slow the ventricular rate, possibly as a result of abnormal electrophysiologic properties of the atrioventricular (AV) node. It has been suggested that patients who tolerate unusually large doses of digitalis probably have a healthy myocardium (3). It remains to be established whether the extremes of tolerance represent some abnormality of metabolism of glycosides or some difference in tissue response. In the vast majority of patients receiving digitalis, the changes in "sensitivity" can be explained adequately by the factors in the following discussion, as well as those listed in Table 1.

The estimated incidence of cardiac toxicity in hospital patients treated with digitalis before the widespread use of serum digoxin and digitoxin concentrations was 12 to 20% (references in reference 4). The determination of serum digoxin concentrations has contributed to decreased incidence of digoxin toxicity (1,2). In a recent study (5) of 437 patients in whom treatment with digitalis was monitored, adverse reactions occurred in 19.5% of patients. However, these reactions were relatively benign, and no deaths were attributed to digitalis (5). This apparent trend toward increasing safety was attributed to better education and improved bioavailability of digoxin, which is the most commonly used digitalis preparation in the United States.

The end point for assessing the drug tolerance is usually the evidence of digitalis toxicity, a condition lacking precise

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Table 1. Certain Factors Modifying Digitalis Tolerance

Possible Reasons for Increased Sensitivity	Possible Reasons for Increased Tolerance
Cardiac	
Increased automaticity of ectopic pacemakers	Decreased automaticity of ectopic pacemakers
Heart disease*	High potassium*
Heart surgery*	Antiarrhythmic drugs†
Low potassium*	Vagal stimulation
Chronic lung disease (?)	Decreased vagal or increased sympathetic activity
Catecholamines and sympathetic stimulation†	Fever, infection, hypoxia, hyperkinetic states (?)
Impaired SAN function and AV conduction	Hyperthyroidism*
Increased vagal activity	Normal infants and young children
Decreased sympathetic activity	Decreased absorption or unusual losses
Heart disease*	Malabsorption
Heart surgery*	Dialysis (?)
Low potassium*	Cardiac bypass (?)
High potassium	
Impaired degradation or excretion	
Hypothyroidism*	
Renal disease*	
Liver disease	
Premature infants*	
Old age (?)	
Interaction with drugs	
Extracardiac	
Allergy and hypersensitivity	
CNS disorders	
Low weight	

*Factors that appear to be of greatest practical importance. †Variable effects. (?) Inconclusive evidence. AV = atrioventricular; CNS = central nervous system; SAN = sinoatrial node.

definition because of the nonspecificity of various "toxic" symptoms. The latter frequently resemble symptoms of underlying heart disease or those of other systems. The long list of toxic digitalis effects includes such nonspecific manifestations as increasing severity of congestive heart failure, acute hemorrhage and necrosis of the intestines, fatigue, headache, vertigo, confusion, depression, delirium and convulsions (references in reference 4).

Similarly, the disturbances of rhythm and conduction caused by digitalis are not specific. Arrhythmia in patients treated with digitalis may be due to the drug, the underlying heart disease, associated metabolic disturbances or treatment with other drugs. The evaluation of digitalis tolerance may be also difficult when different preparations produce different toxic manifestations in the same individual. Thus, the difficulty in the evaluation of digitalis tolerance in patients may be responsible for some of the conflicting and confusing observations reported to date.

The following categories of factors that alter digitalis tolerance will be considered: 1) clinical conditions in which digitalis action may be undesirable, 2) allergy and hypersensitivity to digitalis, 3) physiologic factors modifying tolerance to digitalis, 4) factors that change the amount of digitalis in the body, 5) nervous and metabolic factors modifying tolerance to digitalis, 6) modifications of digitalis tolerance produced by the status of the myocardium, and 7) modifications of digitalis tolerance produced by diseases of organs other than the heart.

Conditions in Which Digitalis Action May Be Undesirable

In patients with hypertrophic cardiomyopathy, the positive inotropic action of digitalis may increase the subaortic obstruction, diminish the effective orifice of the left ventricular outflow tract (6) and contribute to "cavity obliteration." The condition of some of these patients has been shown to deteriorate after digitalis administration and to improve when digitalis is discontinued. Bradycardia due to the vagal action of digitalis may cause a decreased cardiac output in patients with a fixed stroke volume, for example, patients with constrictive pericarditis. Also, the shortening of the refractory period in the accessory AV pathway by digitalis may be harmful in patients with atrial tachycardia or fibrillation or flutter if the atrial impulses are conducted through an accessory pathway with a preexisting short refractory period.

Allergy and Hypersensitivity to Digitalis

Isolated cases of idiosyncratic response to digitalis resulting in urticaria, scarlatiniform exanthema, papules, vesicles, purpura, bullae, angioneurotic edema, eosinophilia or thrombocytopenic purpura have been reported (4,7). Some of the patients allergic to digitalis have positive skin tests for the drug (8).

Physiologic Factors Modifying Tolerance to Digitalis

Age. Children between the ages of 1 month and 2 years tolerate more glycosides per unit of body weight than do older children and adults (4,9–11). This increased tolerance in younger children has been attributed to a greater heart/body weight ratio (12). However, it appears that digitalis requirement is correlated with body surface area rather than weight. Thus, children and adults weighing from 5 to 70 kg require the same therapeutic digitoxin dose per unit of body surface (9).

Premature and newborn infants tolerate less digitalis per unit of body weight than do children between the ages of 1 month and 2 years. The decreased tolerance in premature and young infants has been attributed to immaturity of hepatic and renal function and the resulting impairment of metabolism and excretion (11). The manifestations of digitalis overdosage in children are different from those in adults (12). In children, ventricular ectopic complexes occur less frequently than sinus bradycardia, sinoatrial block and ectopic atrial or AV junctional escape rhythms.

Many clinicians feel that old age lowers digitalis tolerance. Indeed, in old patients, the half-life of digoxin is prolonged as a result of diminished urinary excretion associated with lower creatinine clearance and smaller body size (13). Other factors may also operate. For instance, an age-dependent decrease in the toxic ouabain dose in older rabbits was associated with an apparent increase in ventricular norepinephrine content (14). Age appears to have no significant effect on digitoxin toxicity, probably because elimination of digitoxin is less dependent on kidney function than is elimination of digoxin.

Weight. There is no precise correlation between body weight and tolerance to digitalis. However, there is a general impression that patients with a larger body weight may require larger amounts of digitalis, and that low weight is associated with increased toxicity (15). It has been shown (16) that the dose of ouabain required to produce slowing of the ventricular rate in the presence of atrial fibrillation increases with increasing body weight.

Sex. The estrogen-like effect of digitalis may produce gynecomastia in older men, and an estrogen effect on the vaginal wall in oophorectomized and adrenalectomized mice and postmenopausal women (4). Some investigators suggest that gynecomastia in patients receiving digitalis is either incidental (17) or related to impaired liver function (18). However, prominent bilateral gynecomastia is known to regress within a few weeks after cessation of digitalis therapy (4). There is also suggestive evidence that estrogen may protect against digitalis toxicity. Neutered female dogs treated with estrogenic substances appeared to have a greater tolerance to digitalis than did male dogs or untreated neutered female dogs (4).

There is no uniform agreement about the effect of gender on digitalis. In one study (19) of 179 patients who had absorbed more than 2 mg of digitoxin, the risk of death was higher in men. In a retrospective study (20) comparing young men and premenopausal women with rheumatic valvular disease, the incidence of digitalis-induced arrhythmias was 20.6% in men and 10.2% in women. However, digitalis-induced nausea and vomiting were more frequent in women than in men, possibly indicating a greater sensitivity to digitalis (5).

Blood group. Among digoxin-treated patients, there was a statistically lower incidence of toxicity in patients with blood group O (10%) than in those with groups A, B and AB (16.3%, $p < 0.002$) (21).

Factors That Change the Amount of Digitalis in the Body

The amount of digitalis in the body may be modified by variations in absorption, metabolism, excretion or unusual losses associated with dialysis, bleeding, pregnancy or cardiopulmonary bypass. Left or right ventricular failure does not impair digitalis absorption (22). The metabolism of digoxin is apparently not appreciably altered in patients with a congested liver or alcoholic liver cirrhosis (15,23,24).

Impaired renal excretion. In patients with normal kidney function, urinary renal excretion of digoxin is independent of the glomerular filtration rate (1,2). However, in patients with impaired renal function, digoxin elimination parallels the creatinine clearance. Impaired excretion of digoxin and decreased digitalis tolerance in patients with renal insufficiency have been well documented. Jelliffe and Brooker (25) constructed a useful nomogram for calculating the appropriate doses of digoxin based on renal function and body weight. There are differences between tolerance to digoxin and digitoxin, which is extensively metabolized in the liver. Elimination of digitoxin is less dependent on kidney function, and this favors its use in patients with renal insufficiency.

Jaundice. Patients with jaundice, particularly those with obstructive jaundice, frequently have bradycardia and increased sensitivity to vagal stimulation. This may be due to the effect of the retained bile acids which have a structure similar to that of digitalis. Patients with obstructive jaundice may have hypercholesterolemia. Hypercholesterolemic rabbits appeared to be more resistant to digitalis than did normocholesterolemic animals (26).

Dialysis. The amount of digitalis removed during peritoneal dialysis is small (27). It has been reported (28) that the artificial kidney removes digoxin from plasma only one-

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tenth as effectively as normal kidneys. Blood contains relatively small amounts of digitalis, and no large glycoside losses are expected even with significant hemorrhage. Small amounts of digitalis can cross the placental barrier (29).

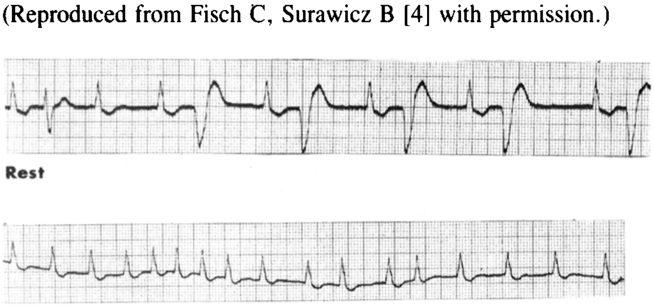
Cardiopulmonary bypass. The loss of digitalis into the pump oxygenator during cardiopulmonary bypass is also small (30), but the effects of cardiopulmonary bypass on digitalis tolerance are controversial. After bypass, undigitalized dogs have been reported to be more sensitive to digitalis, but chronically digitalized dogs required more ouabain to produce an arrhythmia (31,32). In cardiac tissues, radioactivity after cardiopulmonary bypass decreased by 23% in dogs (31) and 10 to 28% in patients (33).

In human patients, myocardial sensitivity to the toxic effects of digitalis was seen to increase in the first 24 hours after cardiopulmonary bypass (33). Toxicity was not related to blood gas and serum electrolyte concentration values, and arrhythmia occurred at serum digoxin levels that were within normal range and lower than those in other patients with arrhythmias due to digitalis toxicity (33).

Nervous Factors Modifying Tolerance to Digitalis

Sympathetic stimulation and catecholamines. Both sympathetic stimulation and catecholamines counteract the antiadrenergic and vagal effects of digitalis. Figure 1 shows an example of such interaction in a patient with atrial fibrillation. At rest, the slow ventricular rate and the ventricular premature complexes appearing as a bigeminal rhythm suggest digitalis toxicity, but after mild exercise the ventricular rate is rapid and ventricular premature complexes are no longer present. Patients who have fever, infection, anxiety or hyperthyroidism, or who are performing exercise require larger than ordinary doses of digitalis to slow the ventricular rate in the presence of atrial fibrillation (4,34). The slowing of ventricular rate produced by digitalis may be reversed to a variable extent by the administration of epinephrine or stimulation of stellate ganglia (4). The catecholamines augment the digitalis-induced increased automaticity of ectopic pacemakers in Purkinje fibers (35,36), and isoproterenol has been used to increase the ventricular rate in patients with digitalis-induced depression of AV conduction.

Figure 1. Electrocardiogram (lead III) of a 38 year old woman with mitral stenosis and atrial fibrillation treated with a daily maintenance dose of 0.5 mg of digoxin. At rest, ventricular ectopic complexes appear partly as bigeminal rhythm. After a 30 yard walk, ventricular rate is rapid and there are no ectopic complexes. (Reproduced from Fisch C, Surawicz B [4] with permission.)



Isoproterenol increased ectopic activity in dogs receiving digitalis. Both catecholamines and excessive doses of digitalis increase the temporal dispersion of excitability recovery and, thus, facilitate ventricular fibrillation. However, there is no convincing evidence that sympathetic stimulation induces ventricular tachycardia or fibrillation in patients receiving digitalis. On the contrary, an intact sympathetic activity appears to protect the myocardium from digitalis-induced vulnerability (37).

Beta-adrenergic blocking agents have been reported to augment the slowing of AV conduction produced by digitalis. They also prevent or suppress digitalis-induced ectopic complexes and rhythms (38), suggesting that digitalis-induced ectopic activity may be somehow related to sympathetic stimulation or catecholamine release. However, the suppression of ectopic activity by the beta-adrenergic blocking agents may be due not to sympathetic blockade, but rather to a direct antiarrhythmic action of these agents (4). Pretreatment with reserpine or guanethidine may prevent the appearance of ectopic complexes or ventricular fibrillation induced by digitalis (4). However, acute or chronic denervation of the heart and catecholamine depletion by reserpine apparently do not alter the dose of digitalis required to produce ventricular ectopic complexes (39,40). As might be expected, the effects of digitalis and reserpine or guanethidine on AV conduction are synergistic, so that smaller doses of digitalis may produce AV block after administration of these agents (41).

In dogs, interruption of cardiac sympathetic innervation by surgical procedures, spinal anesthesia, ganglionic block or pretreatment with reserpine increased toxic and lethal digitalis doses (42–45). Also, after spinal cord transection, the lethal dose of ouabain was higher (43). Spinal cord transection or propranolol treatment delayed the onset of digoxin-induced arrhythmia, but failed to abolish the arrhythmia threshold-lowering effect of left anterior descending coronary artery occlusion in anesthetized cats (44).

Vagal stimulation and ablation. Patients receiving digitalis become sensitive to carotid sinus massage or other types of vagal stimulation (46). Response to carotid sinus stimulation may occasionally provide the earliest evidence of digitalis intoxication by inducing depression of sinoatrial (SA) or AV conduction or by precipitating ventricular ectopic complexes or rhythms (46). The effect of carotid sinus stimulation on the ventricular rate in patients with atrial fibrillation receiving digitalis helps to assess the therapeutic effects of digitalis. Another example of the synergistic action of digitalis and vagal stimulation may be observed during treatment of refractory supraventricular paroxysmal tachycardia, where digitalis becomes effective only after pretreatment with neostigmine.

Removal of parasympathetic innervation to the heart did not modify ouabain toxicity (42). Similarly, bilateral vagotomy did not alter the enhancement of digoxin toxicity caused by ligation of left anterior descending coronary artery disease in the anesthetized cats (44).

Metabolic Factors Modifying Tolerance to Digitalis

Potassium. Increased extracellular potassium concentration inhibits glycoside binding to Na^+-K^+ adenosine triphosphatase (ATPase), decreases the inotropic effect of digitalis (1,2) and suppresses digitalis-induced ectopic rhythms (47). Accordingly, patients with hyperkalemia tolerate large doses of digitalis without developing ectopic activity. Conversely, hypokalemia increases glycoside binding to Na^+-K^+-ATPase and potentiates toxic effects of digitalis (1,2). In the presence of hypokalemia, ectopic complexes and rhythms may appear after the administration of relatively small glycoside doses (48). Also, in patients treated with digitalis, arrhythmias may be precipitated by carbohydrate administration, removal of potassium by dialysis (49–51) and, most frequently, by treatment with diuretic drugs.

The interaction of potassium and digitalis on AV conduction reflects the complex effects of potassium on AV conduction, which may be depressed by both low and high potassium concentrations (52,53). Moderate hyperkalemia may improve AV conduction in patients with digitalis-induced AV block (54), but an opposite effect can occur as a result of a synergistic depressive effect of hyperkalemia on AV conduction, as reported in both dogs and human patients (55–58). Therefore, the net effects of hyperkalemia on AV conduction changes induced by digitalis are not predictable in individual cases. Moreover, these effects depend not only on the absolute plasma potassium concentration, but also on the rate of potassium administration and the structural integrity of the AV junction. In patients with atrial fibrillation treated with digitalis, hyperkalemia frequently causes complete AV block. In patients with preexisting disease of the AV junction, the synergistic effects of hyperkalemia and digitalis on AV conduction may produce severe bradycardia or asystole (59). However, in patients without preexisting AV block, the rate of escape pacemakers is either normal or rapid. Figure 2 shows an electrocardiogram from a patient with atrial fibrillation treated with a daily maintenance dose of 0.25 mg of digoxin. An adequate heart rate is maintained during hyperkalemia, even in the presence of a regular wide QRS rhythm at a plasma potassium concentration of 8.4 mEq/liter.

Hypokalemia may augment digitalis-induced depression of AV conduction. The most characteristic arrhythmias in hypokalemic patients treated with digitalis are ectopic atrial tachycardia with block and nonparoxysmal AV junctional

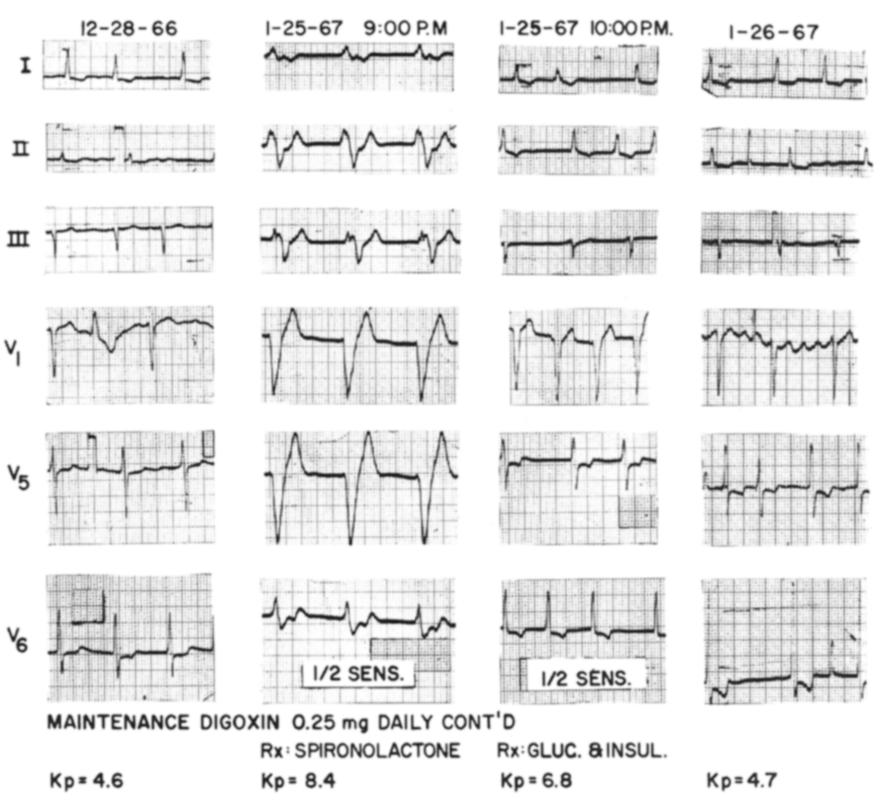


Figure 2. Electrocardiograms of a 58 year old man with atrial fibrillation treated with a maintenance digoxin dose of 0.25 mg daily in the absence (12-28-66) and presence (1-25-67) of hyperkalemia, which was treated with glucose and insulin. Note the regular wide QRS rhythm at a plasma potassium concentration (Kp) of 8.4 mEq/liter. GLUC. = glucose; INSUL. = insulin; SENS. = sensitivity.

tachycardia with or without block; the latter occurs frequently in the presence of atrial fibrillation. These types of arrhythmia are caused by a combination of increased automaticity of ectopic pacemakers and depression of AV conduction.

In general, there is a fairly wide margin of safety between the depressant effects of potassium on AV nodal conduction and automaticity of the escape pacemakers because of the different effects of potassium on AV nodal and His-Purkinje tissue. Thus, cautious administration of potassium is usually safe in the management of serious digoxin-induced arrhythmias which include AV conduction disturbances.

Both hypokalemia and digitalis shorten the effective refractory period of the ventricles and, therefore, shorten the coupling interval of the ventricular ectopic complexes. Slow propagation of early premature ectopic impulses may result in reentry and cause ventricular fibrillation. The synergistic effect of hypokalemia and digitalis on automaticity of ectopic pacemakers and AV conduction explains the low digitalis tolerance of patients with hypokalemia. In these patients, ectopic atrial tachycardia with block or AV junctional tachycardia may appear after the administration of 0.75 to 2.0 mg of digoxin (59). It has been shown that when patients treated with digitalis and diuretic drugs were not receiving potassium supplement, average plasma potassium concentration decreased from 4.3 to 3.4 mEq/liter, total body potassium decreased by 10% and arrhythmias appeared in 50% of the individuals at an average serum digoxin concentration of 1.52 ng/ml (60).

In vitro, increase of automaticity by ouabain due to enhanced phase 4 diastolic depolarization occurred more frequently at $(K^+)o$ of 2.5 m*M*/liter than at 4.0 to 5.0 m*M*/liter (61). In hypokalemic dogs, digoxin toxicity occurred after treatment with a dose that was 39% lower than that in normokalemic animals (62). In hypokalemic dogs with digitalis toxicity, myocardial concentration was 33% less than that of normokalemic dogs. Therefore, enhanced sensitivity was not due to increased digoxin uptake by the heart (62). In another study, hypokalemia induced by glucose and insulin decreased the dose of digoxin required to produce ventricular tachycardia. This was associated with more rapid myocardial digoxin uptake and more rapid Na^+-K^+-ATPase inhibition (63). Toxicity in this setting occurred earlier at a lesser but a more rapidly developing Na^+-K^+-ATPase inhibition as a result of a more rapid glycoside uptake. However, studies (63,64) have also suggested an independent contribution of membrane effects of hypokalemia to digitalis toxicity, in addition to the toxic effects of Na^+-K^+-ATPase inhibition (63,64). Also, the reduced renal excretion of digoxin during hypokalemia contributes to an increased serum digoxin concentration (60).

Calcium. It has been reported that administration of calcium may induce ventricular tachycardia and ventricular fibrillation in patients treated with digitalis (65,66). However, in animals receiving digitalis, hypercalcemia produced ectopic rhythms only when they had received in excess of 95% of the toxic dose of ouabain. Dogs that received 90% of the toxic dose of acetylstrophanthidin had no arrhythmia when serum calcium concentration was 46.2 mg/100 ml (67). In another study (68), AV block occurred in nondigitalized dogs at a serum calcium concentration of 15 to 40 mg/100 ml, and ectopic rhythms terminated in ventricular fibrillation at slightly higher calcium concentrations (68). In that study (68), the effects of calcium in digitalized and nondigitalized animals were similar, and there was no clear evidence of any synergistic or additive effect between calcium and digitalis.

The divergent implications of the early clinical observations and those of the experimental studies in dogs may be due to different rates of intravenous calcium administration. In the study of Nola et al. (69), the amount of acetylstrophanthidin needed to produce arrhythmia was not significantly different from control when serum calcium averaged 12.48 mEg/liter. However, at concentrations higher than 15.0 mEq/liter, less digitalis was needed to produce arrhythmia. Such concentrations are not encountered in clinical practice, but may be achieved during rapid intravenous administration. The study suggests that it is advisable to infuse calcium salts at a slower rate in patients treated with digitalis to avoid marked transient hypercalcemia.

Magnesium. Magnesium-depleted animals appear to be more sensitive to digitalis (70–73). Also, in dogs with hypomagnesemia induced by dialysis utilizing the magnesium-free dialyzate, the dose of toxic arrhythmia was reduced by 26% (74). In dogs with hypomagnesemia induced with furosemide treatment, sustained ventricular arrhythmia and death occurred at significantly lower ouabain doses (75). Hypomagnesemia also enhanced ouabain-induced automaticity in the presence of AV block (75).

In one study (76), hypomagnesemia was present in 21% of patients with and in 10% of those without digitalis toxicity, but this difference was of borderline statistical significance. In other studies, the prevalence of hypomagnesemia in patients with digitalis toxicity (77) was not increased, and there was no correlation between plasma magnesium concentration and serum digitoxin (77) or digoxin (77,78).

Arrhythmias attributed to digitalis toxicity respond favorably to the intravenous administration of magnesium sulfate (79,80), but this does not conclusively establish that arrhythmia is caused by digitalis because of the well known nonspecific antiarrhythmic effect of magnesium salts. It has been shown that in patients in whom magnesium sulfate suppressed digitalis-induced arrhythmias, there was no evidence that the treatment reactivated Na^+-K^+-ATPase, altered myocardial or microsomal digoxin binding or acted through the autonomic nervous system (79).

Acidosis and alkalosis. Since changes in pH are usually associated with altered concentrations of potassium and ionized calcium, the independent effects of acidosis or alkalosis on digitalis tolerance may be difficult to identify (81,82). In anesthetized dogs, metabolic alkalosis (pH 0.757) did not alter the amount of acetylstrophanthidin necessary to produce digitalis toxicity, but prolonged the duration of arrhythmia from an average of 19 to 52 minutes (83). As may be expected, serum potassium concentration was increased by digitalis and decreased by alkalosis.

The mean lethal dose of ouabain was decreased in the presence of both respiratory and metabolic alkalosis (84). This appeared to be independent of hypokalemia because digitalis tolerance remained decreased when hypokalemia was prevented by means of supplemental potassium feeding (84). Also, in patients with metabolic alkalosis and normal plasma potassium concentrations, therapeutic digoxin concentrations (<2.0 ng/ml) were associated with greater arrhythmia prevalence than that in patients without alkalosis (85). The mechanism of the apparent increased sensitivity to digitalis in the presence of alkalosis without hypokalemia is not certain.

Changes in Po_2 and Pco_2. In guinea pigs, the dose of ouabain needed to produce toxic arrhythmia was increased when animals were equilibrated with 100% oxygen at a pressure of 1 atm, and protection increased further at pressures of 2 and 3 atm, an effect attributed to the increased amount of dissolved oxygen in the blood (86).

Similar to digitalis, hypoxia shortens the effective refractory period and may increase automaticity. Dogs breathing hypoxic air mixtures appeared to be more sensitive to acetylstrophanthidin than were dogs breathing room air (87,88). However, the duration of toxic arrhythmia in dogs during ventilation with room air did not differ from that during hypoxia (Po_2 = 40 mm Hg) at the same potassium concentration (87). In contrast to acute hypoxia, chronic hypoxia after a stay of 2 weeks in a hypobaric chamber did not change the average toxic dose of ouabain in conscious dogs (89). The effect of hypercapnia at Pco_2 of 60 mm Hg and lactic acidosis at pH of 7.0 was studied in cats, and neither intervention changed the inotropic response to digitalis (90).

Temperature. The effects of increased temperature are difficult to separate from the effects of increased sympathetic stimulation. Increased body temperature causes an increased heart rate, more rapid AV conduction, a shorter effective refractory period and possibly an increased automaticity of the ectopic pacemakers. More ouabain was required to reduce the ventricular rate of patients with fever than was required in patients without fever (16). However, in dogs, both the toxic and the lethal doses of digitalis were lower at higher body temperature (91).

Moderate hypothermia seems to increase tolerance to digitalis. Larger doses of acetylstrophanthidin were required to induce ectopic complexes in hypothermic dogs (92). Also, the lethal dose of digitalis in cats and dogs with a body temperature reduced to 25 to 28°C was twice as large as in normothermic animals (93,94).

Anesthesia. The results of interaction between anesthetic agents and digitalis in human beings are difficult to evaluate because of the number of factors that may alter the electrophysiologic properties of the heart during operation. The anesthetic agents may have a direct effect on automaticity and conduction, as well as an indirect effect secondary to altered myocardial contractility and ventilation.

In dogs, cyclopropane and digitalis had a synergistic effect on automaticity, thiopenthal did not alter digitalis tolerance compared with awake dogs and halothane increased digitalis tolerance for both toxic and lethal doses (95,96). This increased tolerance induced by halothane persisted after bilateral vagotomy. In pentobarbital-anesthetized dogs, ouabain tolerance was not modified by low and moderate doses of norepinephrine, but was reduced by doses exceeding 1 μg/kg per min (97). Pretreatment with phenobarbital was also observed to enhance digitoxin toxicity in guinea pigs (98). In addition, it has been shown that suxamethonium given for endotracheal intubation may trigger arrhythmias in digitalized patients with coronary artery disease (99), and that succinylcholine may increase digitalis-induced ectopic complexes in animals and human beings (100).

To test the effect of ventilation during anesthesia in dogs anesthetized with pentobarbital and morphine, a group of spontaneously breathing hypoxic, hypercapnic and acidotic animals was compared with a group of artificially ventilated and adequately oxygenated dogs. Toxic and lethal ouabain doses in these two groups were not different from each other, and ouabain toxicity was not altered by pretreatment with propranolol or reserpine in either group (101).

Electric shock. Administration of digitalis decreased the amount of electrical energy required to produce ventricular tachycardia or fibrillation by induction of shock during the vulnerable period (102). Synchronized direct current shock, used for treatment of arrhythmias, frequently precipitated supraventricular and ventricular ectopic complexes and rhythms, including ventricular fibrillation in both animals (103) and patients receiving digitalis (104–106). A more recent study (107) in closed chest dogs, using different doses of digoxin and graded external direct current shocks, showed that despite a wide range of serum digoxin concentration (1.3 to 12.5 μg/ml), the electric shocks caused no electrocardiographic signs of toxicity in any animals. However, in two dogs with manifest electrocardiographic evidence of digitalis toxicity, sustained ventricular tachycardia appeared after electrical shocks at all energy levels. These investigators (107) concluded that the risk of arrhythmia after direct

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current shock is increased in the presence of overt digitalis toxicity, but not after pretreatment with apparently nontoxic digoxin doses.

Status of the Myocardium

Normal versus diseased heart. Healthy adults can tolerate larger amounts of digitalis than can patients with heart disease (17). In young adults without heart disease, excessive doses of digitalis produce the same effects as in children with heart disease, namely, sinus bradycardia, sinus arrhythmia and AV conduction disturbances. Figure 3 shows marked sinus bradycardia, AV conduction disturbances and escape complexes in a young woman who attempted to commit suicide by ingesting large amounts of digoxin. Atropine restored sinus rhythm and shortened the PR interval, suggesting that all the toxic effects of digitalis in this case had been due to vagal stimulation. Figure 4 shows the effect of an excessive dose of digoxin given after operation to a patient with rheumatic heart disease treated before operation with a maintenance dose of 0.1 mg of digitoxin daily. In this patient, digitalis also depressed AV conduction and induced an ectopic ventricular rhythm. However, the rate of the ectopic pacemaker is more rapid than the rate of the escape pacemaker in the patient without heart disease. Ordinary therapeutic doses of digitalis frequently augment or induce ectopic activity in patients with heart disease (108).

Cardiac surgery. Evaluation of the relation between arrhythmia and digitalis after cardiac surgery is difficult because, in these patients, the effects of digitalis are frequently superimposed on the effects of anesthesia, metabolic abnormalities, fever, surgical trauma and other factors (references in reference 4). In one study (99), the frequency of perioperative arrhythmias was not increased by preoperative treatment with digitalis in patients with coronary artery disease undergoing abdominal surgery.

A review of records of approximately 400 patients treated with digitalis after cardiac surgery (4) showed that the ventricular rate was usually more rapid after operation than before, even when the postoperative maintenance dose of digitalis was unchanged. The ventricular rate remained rapid in patients with fever, infection, pulmonary embolism and post-pericardiotomy syndrome, even when the maintenance dose of digitalis was increased. In 11 patients with atrial fibrillation, ventricular rate in excess of 100 beats/min persisted for 2 months to 2 years, even when the maintenance dose of digoxin was as high as 0.75 mg or 1.0 mg daily. Of these 11 patients, 10 had intermittent fever due to pulmonary emboli, pneumonia, pleurisy or postpericardiotomy syndrome, and 1 had hyperthyroidism. This study (4) suggests that the increased requirement of digitalis in such patients need not be attributed directly to the operation.

Myocardial infarction. In cats, sensitivity to digitalis remained unchanged early after coronary artery ligation (109),

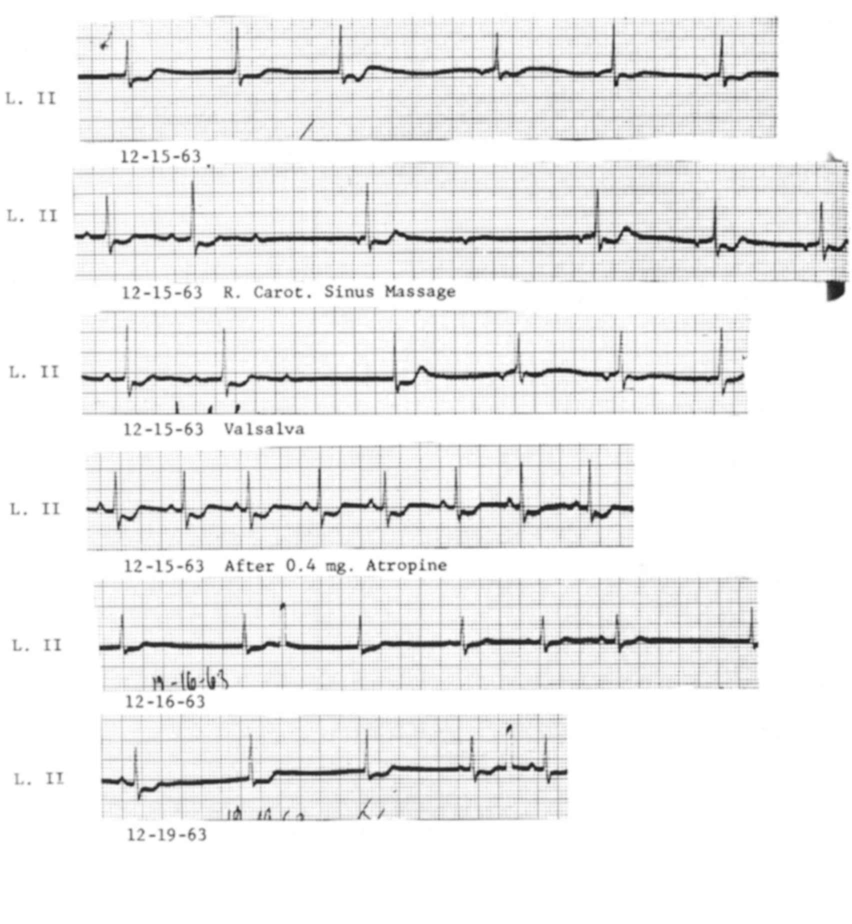


Figure 3. Electrocardiogram of a 17 year old woman after she attempted to commit suicide by ingesting 3.0 to 4.0 mg (30 to 40 tablets) of digitoxin. **Upper three strips**, recorded on the day of ingestion, demonstrate depression of sinoatrial (SA) node activity, supraventricular escape complexes and slowing of ventricular rate after right carotid (R. Carot.) sinus massage and after the Valsalva maneuver. **Fourth strip**, recorded on the same day, shows regular sinus rhythm with a rate of 90 beats/min and a normal PR interval after intravenous administration of 0.4 mg of atropine sulfate. **Two lower strips**, recorded 1 and 4 days after digitoxin ingestion, demonstrate persistent depression of SA node activity and supraventricular escape complexes. (Reproduced from Fisch C, Surawicz B [4] with permission.)

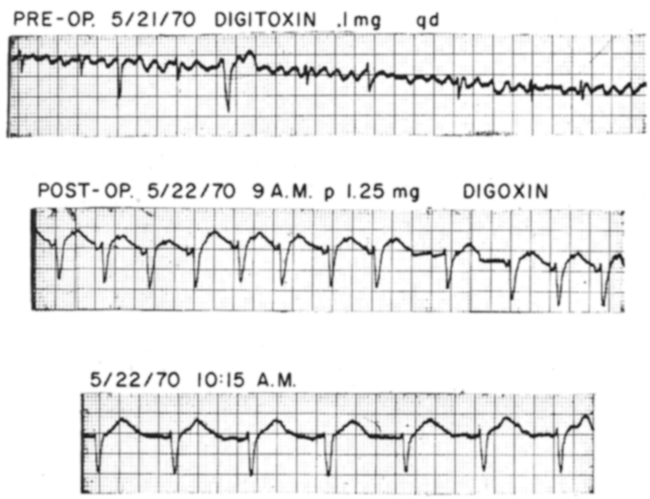


Figure 4. Electrocardiogram (lead III) of a patient with rheumatic heart disease and atrial fibrillation treated with a daily 0.1 mg maintenance dose of digitoxin. Before operation (PRE-OP.) (**upper strip**), well controlled ventricular rate and occasional ventricular premature complexes are seen. After mitral and tricuspid valve replacement (POST-OP.), the patient received 1.25 mg of digoxin intravenously. Note ventricular tachycardia at 9:00 AM and a slower regular ventricular rhythm, possibly due to exit block, at 10:15 AM.

but increased in the stage of healing infarction (110). In dogs, digitalis tolerance was decreased early after ligation of a coronary artery and in the stage of chronic myocardial infarction (111). Patients after myocardial infarction appeared to tolerate the usual therapeutic doses of digitalis (112) without increase in the incidence of arrhythmias after digitalis administration. However, in patients with sick sinus syndrome, caution should be used when administering digitalis (113).

During evolution of experimental myocardial infarction in pigs, the average toxic dose of acetylstrophanthidin was reduced by approximately 20% and the digitalis-induced arrhythmias lasted twice as long as in control or sham-operated animals (114). In conscious dogs, tolerance to acetylstrophanthidin decreased within 1 hour after myocardial infarction by 24%, but returned to control during the healing phase 1 week later (115). Studies in vitro (116) have shown that in cardiac fibers depolarized to a level positive to −65 mV, glycosides facilitate undamped oscillatory activity. This finding could explain the increased prevalence of toxic arrhythmias in diseased depolarized myocardium.

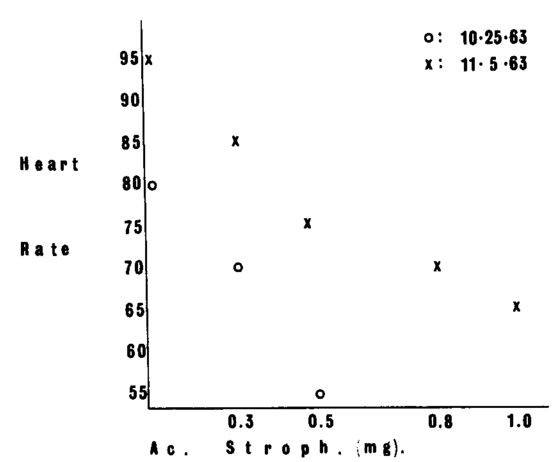
In a randomized study (117) of patients with acute myocardial infarction, treatment with ordinary therapeutic doses of digoxin did not change the incidence or type of ventricular arrhythmias during the 3 hours after drug administration, and there was no evidence that myocardial infarction caused an increased sensitivity to ordinary doses of digoxin at serum digoxin concentrations averaging 1.9 ± 0.7 ng/ml. In another study (15), the incidence of digitalis toxicity in patients with heart disease, including cardiomyopathy, increased only when their New York Heart Association functional class was III or IV.

Diseases of Other Organs

Chronic lung disease. There is no agreement about the digitalis tolerance in patients with chronic pulmonary insufficiency. In one of the early studies (118), 31% of 122 digitalis-treated patients with chronic cor pulmonale and no evidence of other heart disease had arrhythmias that were predominantly supraventricular. In another study (119), 1.32 mg of acetylstrophanthidin was administered to 29 patients with chronic pulmonary insufficiency. Of these, eight patients who appeared to have evidence of increased sensitivity to digitalis were more severely hypoxemic than the patients without such evidence. These observations suggested an increased sensitivity to digitalis in the presence of hypoxia. In another study (120), patients with chronic obstructive lung disease and severe hypoxemia (Po_2 of 31 to 42 mm Hg) had arrhythmias consistent with digitalis toxicity at lower than toxic digoxin and digitoxin blood concentrations. However, other studies (15) showed no evidence of increased digitalis toxicity in patients with chronic lung disease.

Patients with cor pulmonale frequently have ectopic supraventricular complexes and rhythms. In such patients, normal digitalis doses may increase the rate of ectopic pacemakers, produce variable degrees of AV block and simulate digitalis toxicity. Digitalis toxicity may be induced by the

Figure 5. Results of two acetylstrophanthidin tolerance tests in a patient with myxedema, mitral stenosis and atrial fibrillation before (○) and after (x) treatment with triiodothyronine. The dose of acetylstrophanthidin (Ac. Stroph.) in mg is shown on the **abscissa**, and the ventricular rate per minute on the **ordinate**. The control rate is 80 beats/min before and 95 beats/min after 11 days of treatment. Note that before treatment, 0.5 mg of acetylstrophanthidin slows the ventricular rate to 55 beats/min, but after treatment the dose of acetylstrophanthidin needed to slow the ventricular rate to 65 beats/min is two times larger.



use of excessive doses given in an attempt to slow the ventricular rate in patients with pulmonary disease and sinus tachycardia.

We analyzed some of the factors that precipitated digitalis toxicity in 12 patients with severe pulmonary insufficiency, hypercapnia and severe arterial oxygen unsaturation (4). Of these 12 patients, digitalis induced atrial tachycardia with block in 6, AV junctional tachycardia in 3 and multiple ventricular ectopic beats in the remaining 3. We found that of these 12 patients, 5 had received excessive doses of digitalis administered in an attempt to slow the sinus rate, 5 patients had hypokalemia and 1 had renal insufficiency. In only 1 of the 12 patients was there an adequate explanation for the apparently decreased digitalis tolerance. Personal observations suggest that in patients with chronic cor pulmonale, hypoxia seldom causes decreased tolerance in digitalis. In a comprehensive review of the use of digitalis in patients with pulmonary disease, Green and Smith (121) pointed out that the studies of digoxin turnover in patients with cor pulmonale revealed no evidence of changes in drug metabolism and, thus, no basis for increased sensitivity. The authors concluded that the following three questions still need to be answered: 1) Is the frequency of arrhythmia in patients with chronic lung disease increased in the presence of therapeutic levels of cardiac glycosides? 2) Is there any correlation between arrhythmia and concurrent use of sympathomimetic drugs used to treat chronic lung disease? 3) Do patients with stable chronic lung disease have an increased occurrence of digitalis toxicity when the severity of lung disease, the underlying heart disease and other factors predisposing to cardiac arrhythmias are taken into account?

Hypo- and hyperthyroidism. *Hypothyroidism.* The thyroid function modifies the metabolism of digitalis (6). Patients with hypothyroidism are said to be more "sensitive" and patients with hyperthyroidism more "resistant" to digitalis. In patients with hypothyroidism small doses of digitalis may depress the sinus rate and AV conduction considerably. Many hypothyroid patients with atrial fibrillation do not require digitalis or other drugs to control the ventricular rate (122). In others, rate control can be achieved by using smaller than customary therapeutic doses. Figure 5 shows the results of an acetylstrophanthidin tolerance test in a patient with myxedema, mitral stenosis and atrial fibrillation not treated with digitalis. The control ventricular rate was 80 beats/min. After the administration of 0.5 mg of acetylstrophanthidin, the rate decreased to 55 beats/min and ventricular premature complexes appeared. After 17 days of treatment with triidothyronine and no digitalis, the control ventricular rate was 95 beats/min, and a dose of 1.0 mg of acetylstrophanthidin was required to decrease the rate to 65 beats/min without appearance of ventricular premature complexes.

Hyperthyroidism. Customary therapeutic doses of digitalis produce no effect on the ventricular rate in hyperthyroid patients with atrial fibrillation. Beta-adrenergic blocking agents are needed frequently to achieve an adequate slowing of ventricular rate. Hyperthyroid patients may tolerate larger than customary therapeutic doses of digitalis, but the safety of such therapy may be questioned. In hyperthyroid cats, treatment with digitalis produces myocardial necroses, but the clinical pertinence of this observation is not certain. There is no agreement about the mechanisms by which the thyroid function alters digitalis tolerance. In one study (123), the excretion rates and the serum half-life of digoxin appeared to be the same in hypo-, hyper- and euthyroid patients. Therefore, the differences in digoxin concentrations were attributed to differences in the space of glycoside distribution, possibly as a result of differences in Na^+-K^+-ATPase activity (1). However, in another study (124), differences in serum digoxin concentration correlated with differences in creatinine clearance, which was increased in hyper- and decreased in hypothyroid patients. Since the digoxin half-life was inversely proportional to creatinine clearance, the differences in digitalis tolerance could be attributed to faster glycoside elimination in patients with hyperthyroidism and slower elimination in those with hypothyroidism (124).

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